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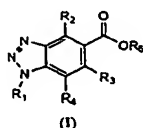
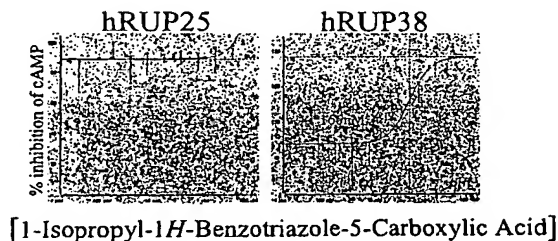
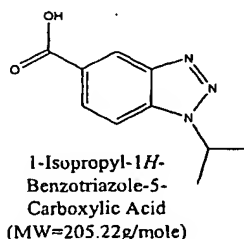
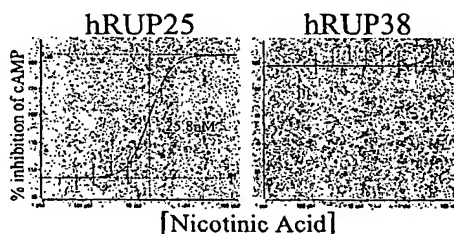
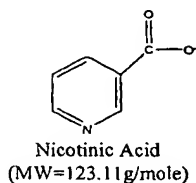
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[Continued on next page]

(54) Title: BENZOTRIAZOLES AND METHODS OF PROPHYLAXIS OR TREATMENT OF METABOLIC-RELATED DISORDERS THEREOF

Screening Data for Nicotinic Acid and 1-Isopropyl-1H-Benzotriazole-5-Carboxylic Acid in cAMP Assays



(57) Abstract: The present invention relates to certain benzotriazole carboxylic acid or ester derivatives of Formula (I), pharmaceutically acceptable salts and solvates thereof, which exhibit useful pharmaceutical properties, for example, as agonists for the GPCR referred to as hRUP38. Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the prophylaxis or treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of -glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers and the like.



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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 794 184 A (DAINIPPON PHARMACEUTICAL CO) 10 September 1997 (1997-09-10) Formula (III) wherein R2a is ethyl page 7, line 15 - line 30 ---	1, 4-8, 12
A	EP 1 247 810 A (PFIZER PROD INC) 9 October 2002 (2002-10-09) claim 1 -----	1-25



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Johnson, C

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International application No.
PCT/US 03/35427

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/35427

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0794184	A	10-09-1997	AT 201679 T	15-06-2001
			AU 695490 B2	13-08-1998
			AU 3856395 A	17-06-1996
			BR 9509800 A	30-09-1997
			CZ 9701540 A3	15-10-1997
			DE 69521142 D1	05-07-2001
			DE 69521142 T2	13-09-2001
			DK 794184 T3	30-07-2001
			EP 0794184 A1	10-09-1997
			FI 972129 A	18-07-1997
			GR 3036226 T3	31-10-2001
			HK 1001395 A1	21-09-2001
			NO 972111 A	21-07-1997
			NZ 295259 A	27-05-1998
			PL 320294 A1	15-09-1997
			RU 2141958 C1	27-11-1999
			SI 794184 T1	31-08-2001
			SK 61597 A3	05-11-1997
			US 5932568 A	03-08-1999
			CA 2205523 A1	30-05-1996
			CN 1173177 A , B	11-02-1998
			ES 2156950 T3	01-08-2001
			HU 77316 A2	30-03-1998
			IL 116012 A	30-11-1999
			WO 9616059 A1	30-05-1996
			JP 3222051 B2	22-10-2001
			JP 8208643 A	13-08-1996
			JP 8225571 A	03-09-1996
			PT 794184 T	28-09-2001
			TW 419478 B	21-01-2001
			ZA 9509825 A	27-05-1996
EP 1247810	A	09-10-2002	BR 0201087 A	27-05-2003
			CA 2379903 A1	04-10-2002
			EP 1247810 A1	09-10-2002
			JP 2002308872 A	23-10-2002
			US 2003078432 A1	24-04-2003

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